

Developmental Twin Studies of Relations Between Substance Use and ADHD

Jim Hudziak, M.D.

University of Vermont, College of Medicine

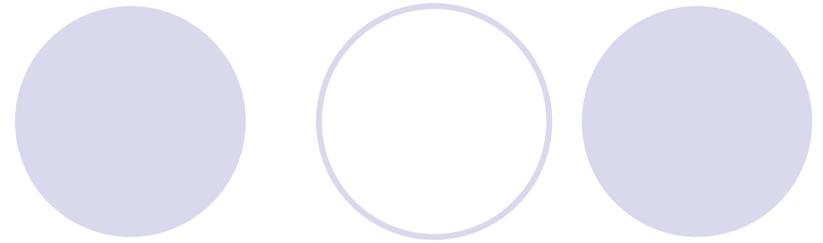
Dorret Boomsma, Ph.D.

Vrije Universiteit, Amsterdam, The Netherlands

Rich Todd, Ph.D., M.D.

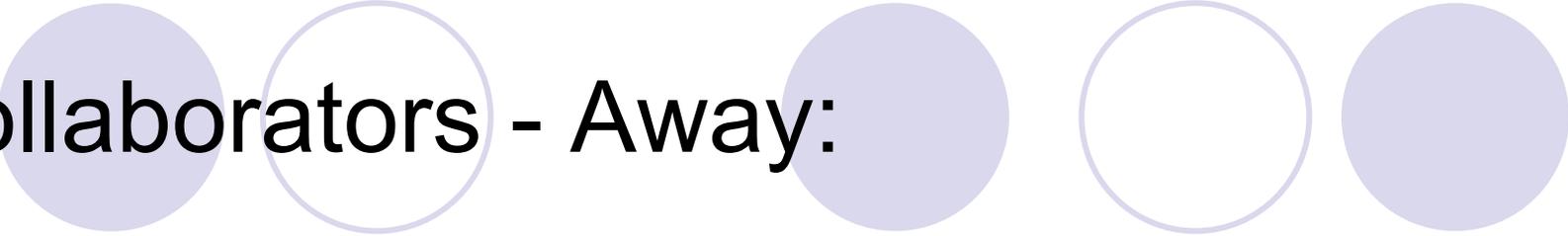
Washington University, St. Louis, MO.

Collaborators:

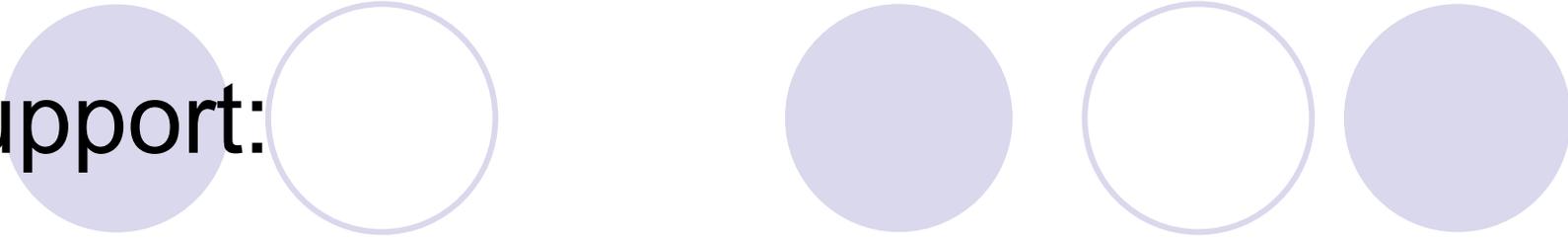


- Dorret Boomsma, Ph.D. Director of our group and the Netherlands Twin Registry, Vrije University, Amsterdam, The Netherlands.
 - Meike Bartels, Ph.D.
 - M. Rietveld, Ph.D.
 - T. van Beijsterveldt, Ph.D.
 - Eske Derks
- Vermont
 - Cathy Stanger, Ph.D
 - David Rettew, M.D.
 - Rob Althoff, Ph.D., M.D.
 - Bill Copeland, Ph.D.

Collaborators - Away:



- Richard Todd, Ph.D., M.D. Washington University.
- Andrew Heath, D. Phil., Washington University

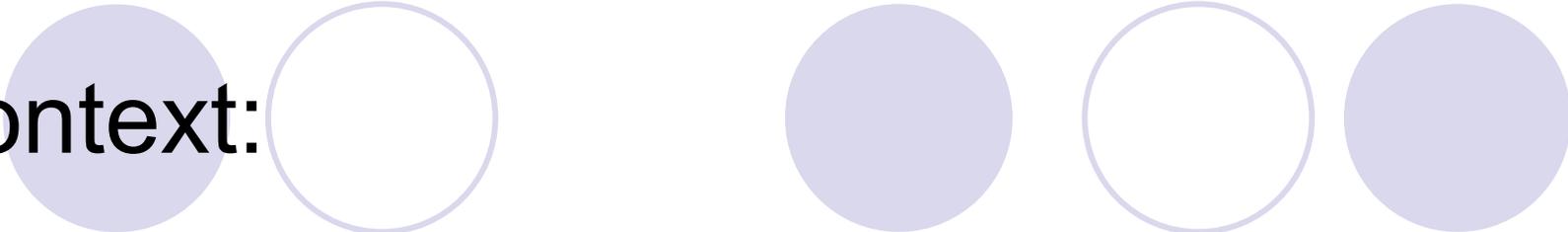


Support:

- National Institutes of Health, NIH grant RO1 MH58799-03. Developmental twin study of attention, aggression, and affect.(JH)
- Spinoza and NWO 575-25-006 grants to D. Boomsma.

Outline:

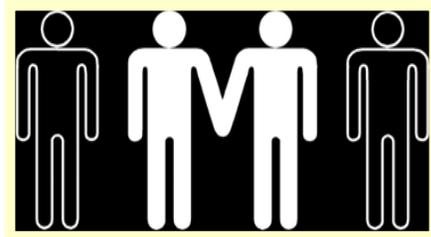
- Introduction
- The Child Behavior Checklist (CBCCL).
- Multi-Informant Cross-Sectional Data on AP, AGG, and RB.
- Longitudinal Data on AP and AGG.
- Comorbidity Data AGG/RB.
- Maternal Smoking Data and AP and AGG.
- Longitudinal Latent Class Approaches on ADHD Data.
- Discussion.



Context:

- Maternal Smoking increases the risk for child psychopathology (ADHD, ODD, RB (DB)).
- Child Psychopathology increases risk for Alcohol and cigarette use.
- But in which specific children?
- What about persistence?

Netherlands Twin Register



25,000 twin pairs registered at birth, born after

1986

Questionnaire variables

Zygoty, health and growth

2, 3, 5, 7, 10, 12

SES

3, 7, 10, 12

Problem behavior

CBCL (Devereux at 5)

3, 5, 7, 10, 12

TRF

7, 10, 12

YSR

12

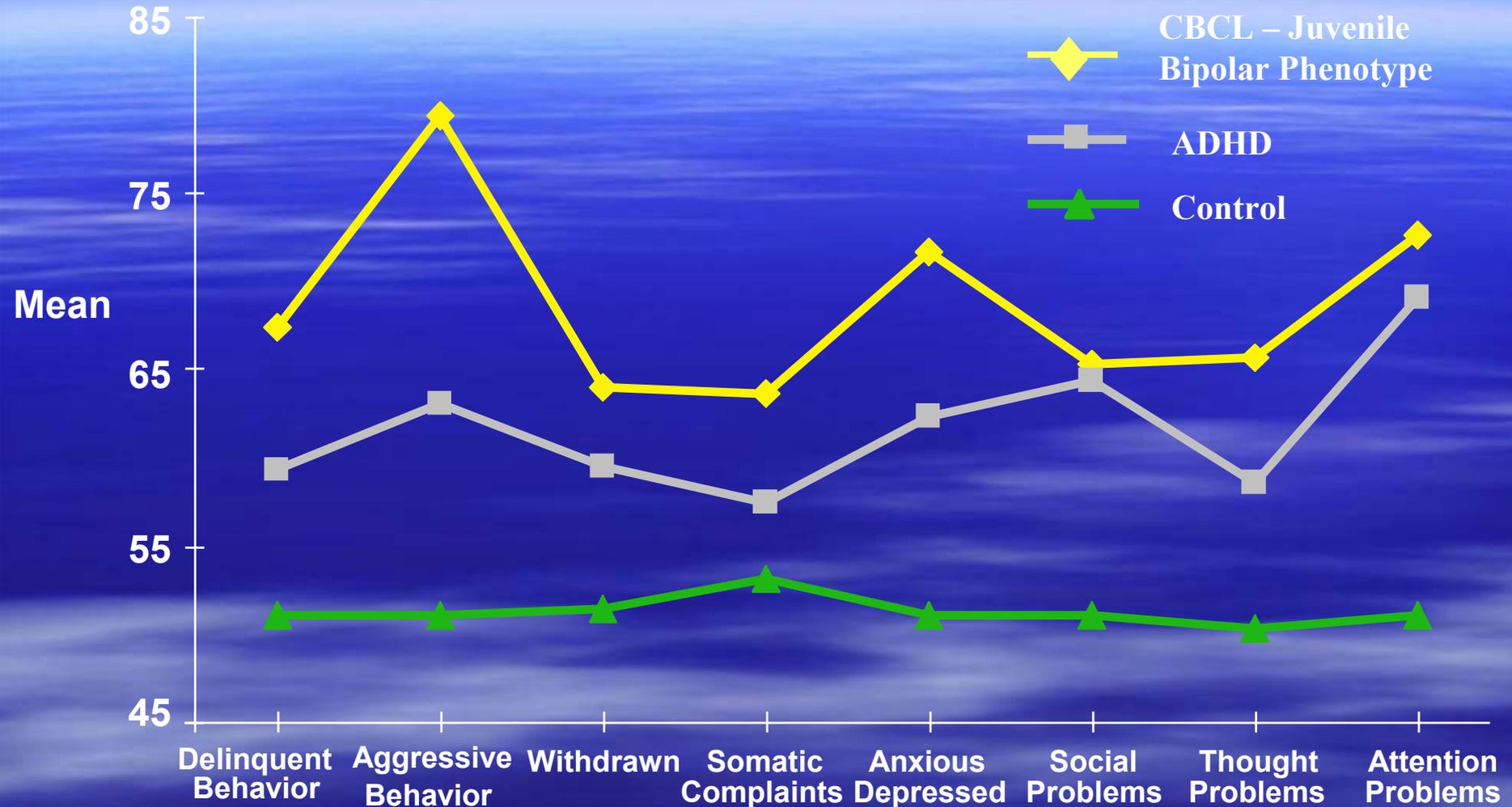
Conners ADHD-I and ODD data

7, 10, and 12

What is the Child Behavior Checklist?

- 118 items of common behavior
- Reported on by mothers, fathers, teachers (Teacher Report Form), and children (Youth Self Report).
- Scored 0,1,2.
- Factor analyzed
- 8 Syndromes (AP,AGG, A/D)

CBCL Clinical Scales

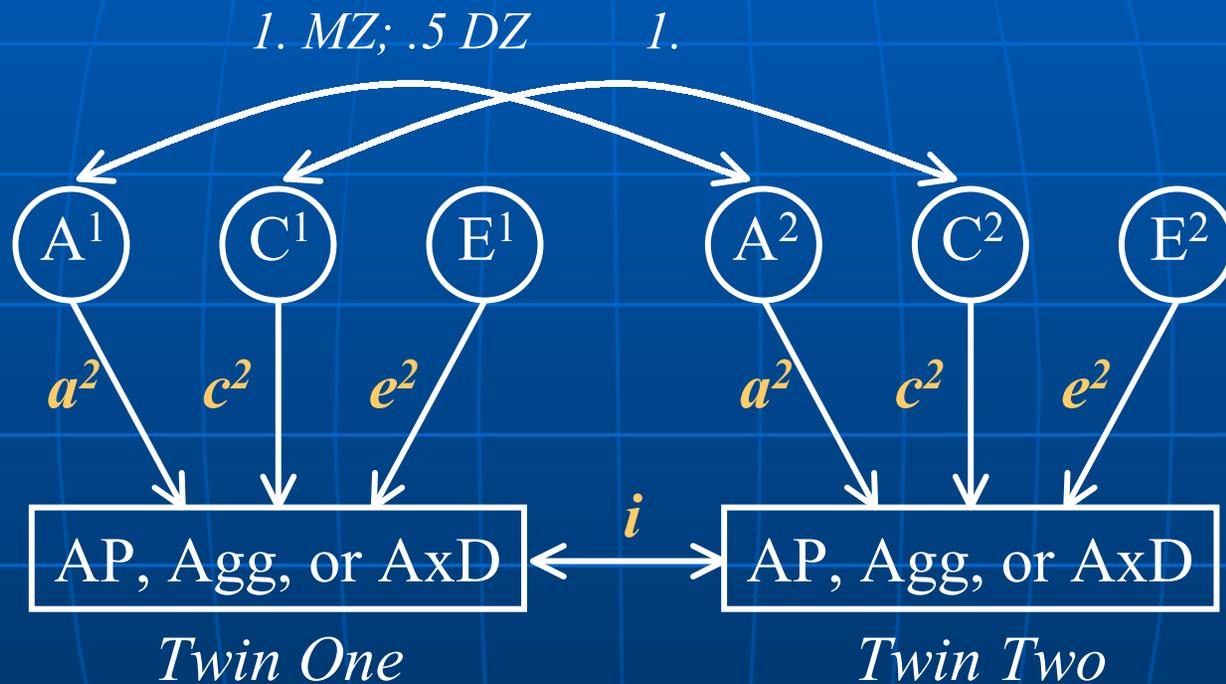


CBCL-DSM Predictive Relations

- AP - ADHD (93%)
- AGG - ODD/CD, (95%)
- AGG + DB - CD (92%)

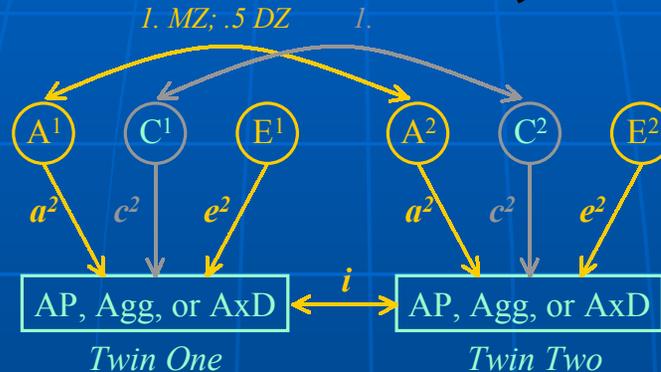
- *Biederman et al (1992), Steingard et. Al (1994), and Chen et al. (1994), have all published similar results.*

Univariate AGG, AxD, & AP



Data: CBCL. N Pairs: 84 MZM; 118 DZM; 68 MZF; 98 DZF

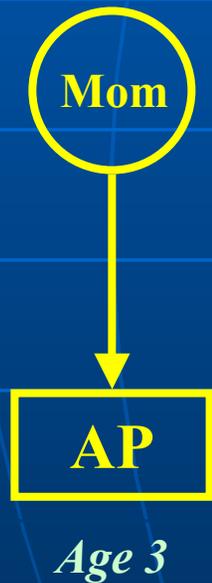
Univariate AGG, AxD, & AP



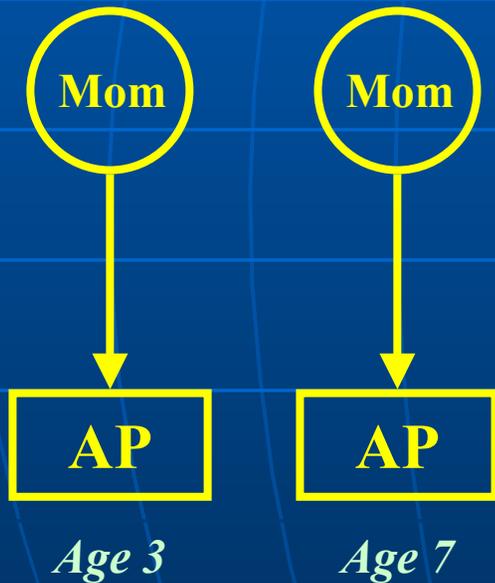
Syndrom		X^2	df	p	a^2	e^2	i
<i>e</i>							
AP:	M	1.30	3	.73	.77	.23	-.0
AP:	F	2.21	3	.53	.70	.30	-.0
AxD:	M	2.17	4	.70	.65	.35	*
AxD:	F	1.52	4	.82	.61	.39	*
Agg:	M	6.34	3	.10	.69	.31	.0
Agg:	F	5.97	4	.20	.70	.30	*

* *ci's encompass 0*

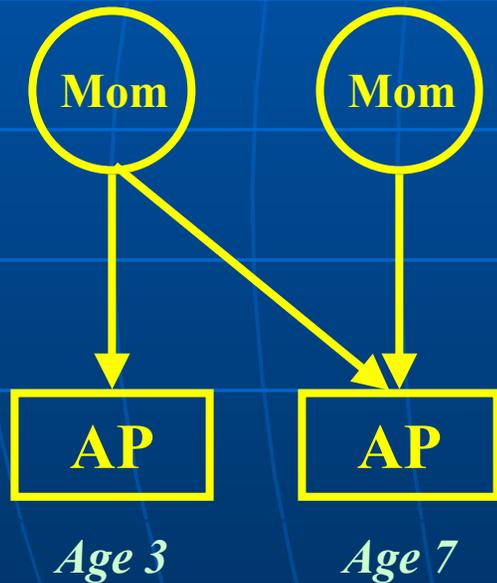
Developmentally Sensitive Analysis



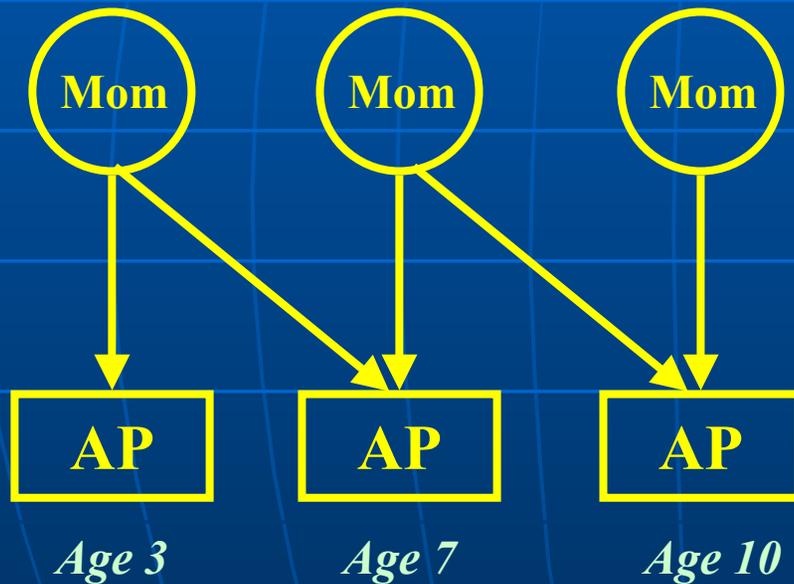
Developmentally Sensitive Analysis



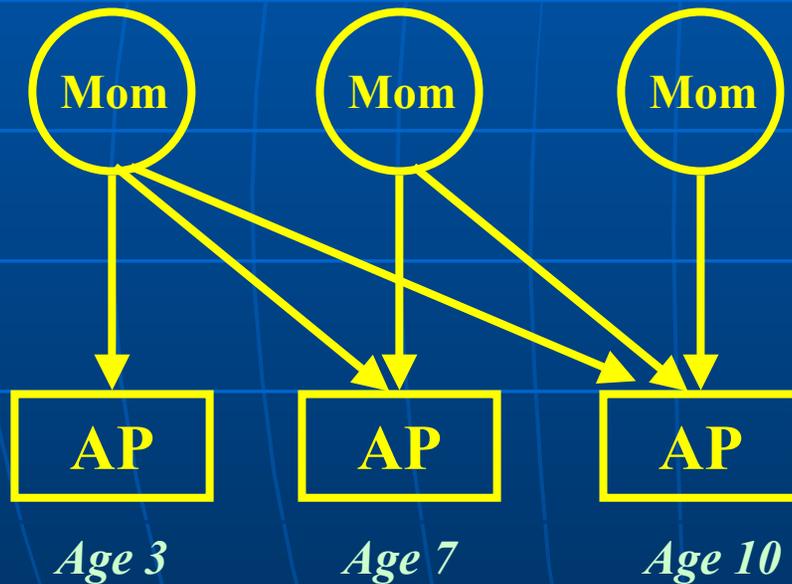
Developmentally Sensitive Analysis



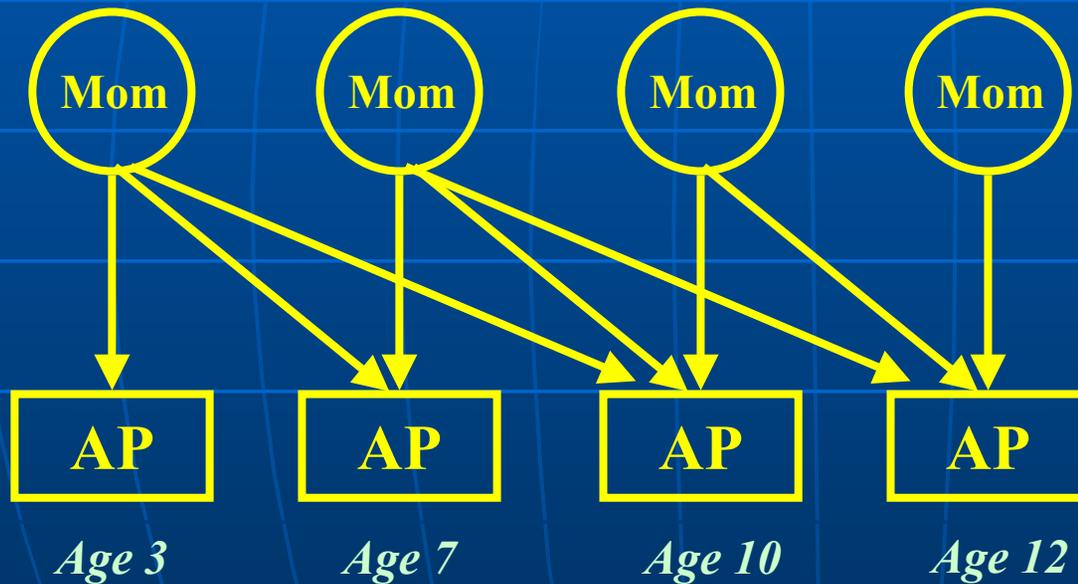
Developmentally Sensitive Analysis



Developmentally Sensitive Analysis



Developmentally Sensitive Analysis



Heritability of attention problems in children: Cross sectional results from a study of twins, age 3-12 years.

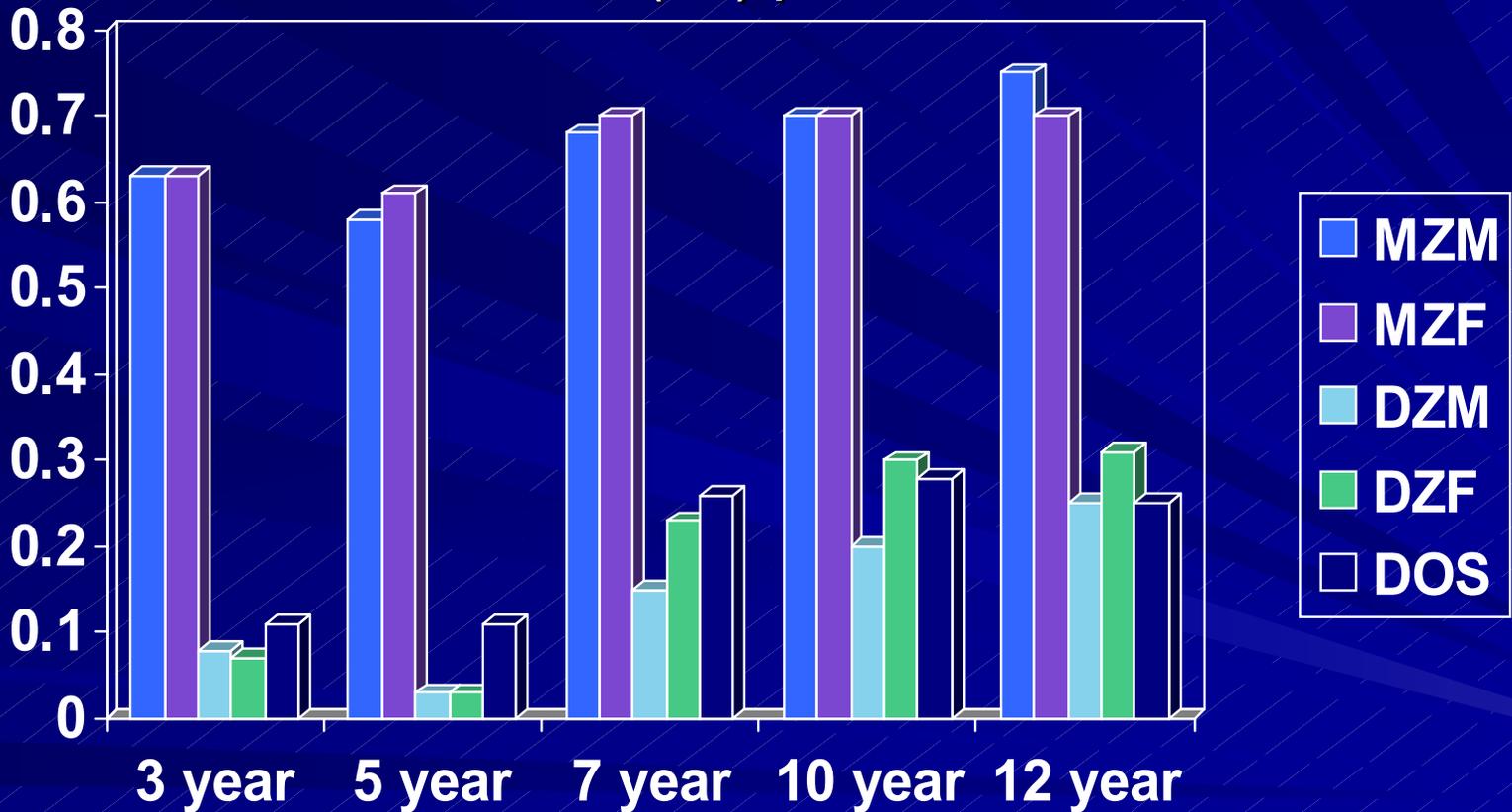
- Rietveld, M. J., Hudziak, J. J., Bartels, M. Van Beijsterveldt, C. E., Boomsma, D. I. (2003a). *Am. J. Med. Genet.* **117B**:102-112.

CBCL/4-18 for 7-, 10-, and 12-year-olds

Attention problems [AP]

- 1. Acts too young for his/her age
- 8. Can't concentrate, can't pay attention for long
- 10. Can't sit still, restless, or overactive
- 13. Confused or seems to be in a fog
- 17. Daydreams or gets lost in his/her thoughts
- 41. Impulsive or acts without thinking
- 45. Nervous or tense
- 46. Nervous movements or twitching
- 61. Poor school work
- 62. Clumsy or poorly coordinated
- 80. Stares blankly

Dutch twin correlations: Mother ratings for overactive behavior (3 yr), 5-item attention (5 yr), CBCL attention problems (7, 10, 12 yr); total N = 3835 (3), 6660 (5), 3427 (7), 2504 (10) and 1307 (12) pairs.



Longitudinal of AP

- Broad heritability of AP are estimated at nearly 75%, at each age. The results indicated revealed less stability at age 3 to AP at age 7 ($r = .40$), compared to the stability from AP at age 7 and beyond ($r = .70$). **Genetic effects were found to explain between 70% of the variance across development.**
- AP is found highly heritable at all ages in both genders. The same set of genes appears to be expressed in boys and girls.
- The genetic and environmental contributions remain stable across the ages studied. **Stability AP is accounted for by genetic influences.**
- Children who do not display AP at a given age are unlikely to develop these problems at a subsequent age.

Individual Differences in Aggression: Genetic Analyses by age, gender, and informant in 3-, 7-, and 10-year-old Dutch Twins.

- Hudziak, J.J.,¹ van Beijsterveldt, C.E.M.,² Bartels, M.,² Rietveld, M.J.H,² Rettew, D.C.¹, Derks, E.M.² and Boomsma, D.I.

■ In Press, Behavioral Genetics, 2003

Items in other report C B C L₆₋₁₈

- Argues
- Bragging
- Mean to others
- Demands attention
- Destroys own things
- Destroys others' things
- Disobedient at home
- Disobedient at school
- Jealous
- Gets in fight
- Attacks
- Screams a lot
- Showing off, clowning
- Stubborn
- Mood changes
- Talks too much
- Teases a lot
- Temper
- Threatens others
- Loud

Results Cross-Sectional AGG

- Differences in raw scores across gender were found, with boys being rated as more aggressive than girls by all informants. Mothers reported more symptoms than fathers, who reported more symptoms than teachers. **Evidence for moderate to high genetic influence (51% to 72%) was seen for AGG by all three informants at all ages** with only small sex differences in heritability estimates, except for teacher reports on girls.
- Teachers on girls, yields evidence of genetic dominance.
- Best fitting models for AGG by parent reports also included a small contribution of common environment. The largest sex differences in heritabilities were seen at age 10. Contributions of common (13% to 27%) and unique (16-31%) environment were small to moderate. There was some evidence of genetic dominance by teacher report for 10-year-old girls.
- **Although M, F, and T reports only correlated $\sim .38\%$, all informants identify genetic influences exceeding $.68\%$.**

Causes of stability of aggression from early childhood to adolescence: A longitudinal genetic analysis in Dutch twins

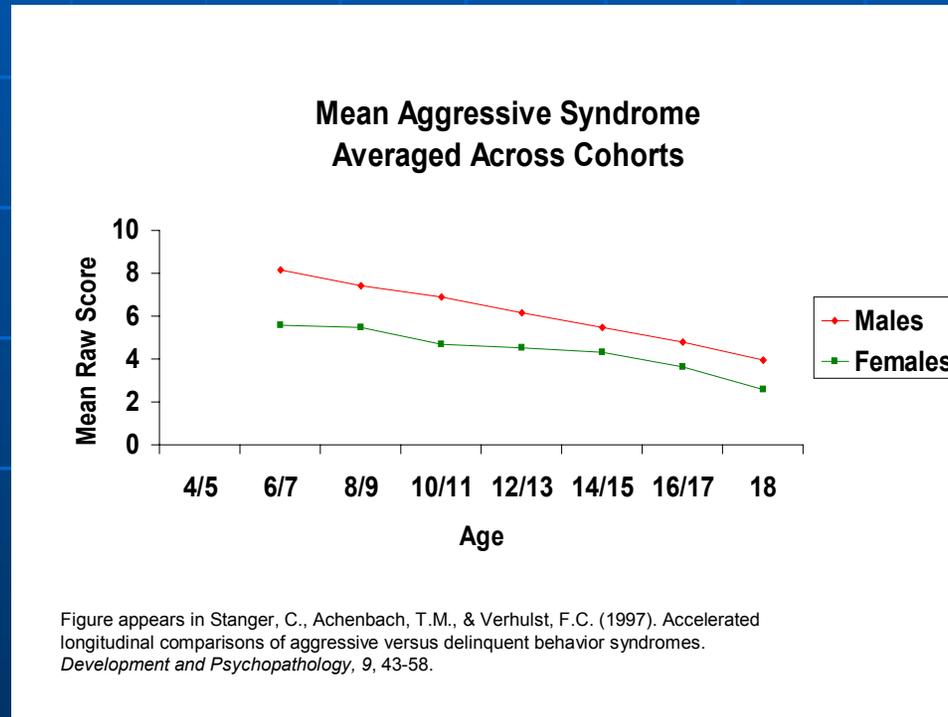
van Beijsterveldt, C.E.M.¹, Bartels, M.¹, Hudziak,
J.J.² and Boomsma, D.I.¹

¹Department of Biological Psychology, Vrije
Universiteit, Amsterdam, The Netherlands.

²Department of Psychiatry and Medicine (Division of
Human Genetics), Center for Children, Youth and
Families, and University of Vermont, College of
Medicine, Burlington, USA

In Press. *Journal of Behavioral Genetics*, 2003

Behavior Changes over Time:



Stability:

- AGG showed moderate to high stability during childhood. The stability coefficients ranged from 0.41 to 0.77 across varying intervals. Averaged across boys and girls, **genetic factors accounted for approximately 65% of the total stability.**
- On average, 6-8% of the children meet clinical severity criteria.
- Longitudinal genetic analysis indicated a simplex model for genetic effects, **which suggest a dynamic development process consisting of transmission of existing genetic effects interacting with new genetic influences.** In conclusion, these data support the idea that both genetic and environmental influences play a role in the stability of AGG from age 3 to 12.

Delinquent Behavior (Now Rule Breaking)

- Rule Breaking syndrome behaviors are as they sound. These are kids who break rules. Operationally are similar to T Moffitt's adolescent limited conduct disorder type. Indeed, RB is predictive of DSM CD diagnosis.
- Rule Breaking Behavior (formally, delinquent behavior) has been shown to be most predictive of adolescent substance use. Stanger et al, 2000.

Mean Delinquent Syndrome Averaged Across Cohorts

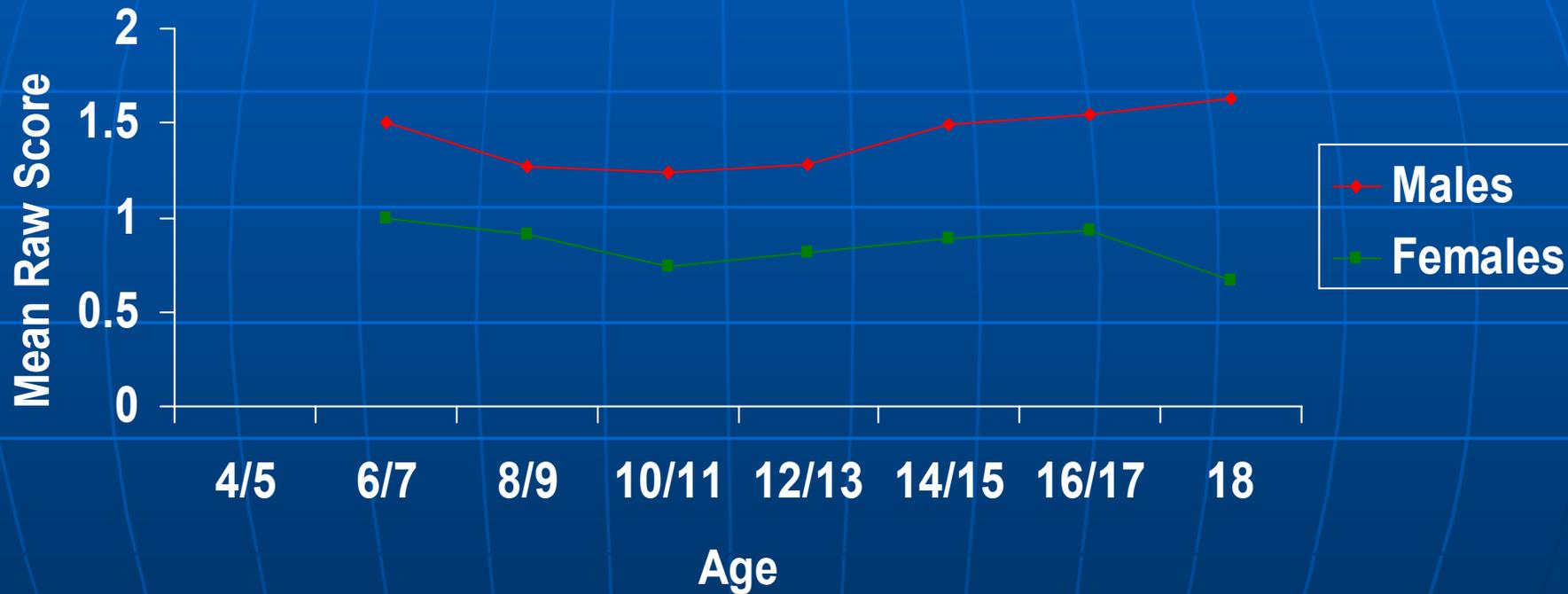


Figure appears in Stanger, C., Achenbach, T.M., & Verhulst, F.C. (1997). Accelerated longitudinal comparisons of aggressive versus delinquent behavior syndromes. *Development and Psychopathology*, 9, 43-58.

Results for DB/RB at Age 7, 10, & 12

	MOM			DAD			
Age	A	C	E		A	C	E
7	.50 (.42-.56)	.30 (.25-.37)	.20 (.19-.22)	7	.60 (.53-.67)	.24 (.23-.30)	.16 (.15-.18)
M 10	.62 (.60-.64)	.22 (.16-.29)	.16 (.14-.18)	10	.62 (.53-.70)	.21 (.13-.30)	.17 (.14-.19)
12	.60 (.46-.71)	.23 (.13-.36)	.17 (.15-.21)	12	.53 (.40-.67)	.32 (.19-.45)	.15 (.12-.18)
	A	C	E		A	C	E
7	.34 (.33-.43)	.44 (.36-.51)	.22 (.20-.28)	7	.33 (.32-.45)	.43 (.32-.50)	.24 (.21-.26)
F 10	.23 (.11-.33)	.52 (.42-.62)	.25 (.22-.29)	10	.34 (.21-.47)	.43 (.30-.55)	.24 (.20-.26)
12	.36 (.30-.54)	.39 (.32-.54)	.21 (.20-.30)	12	.47 (.31-.61)	.31 (.17-.45)	.22 (.19-.27)

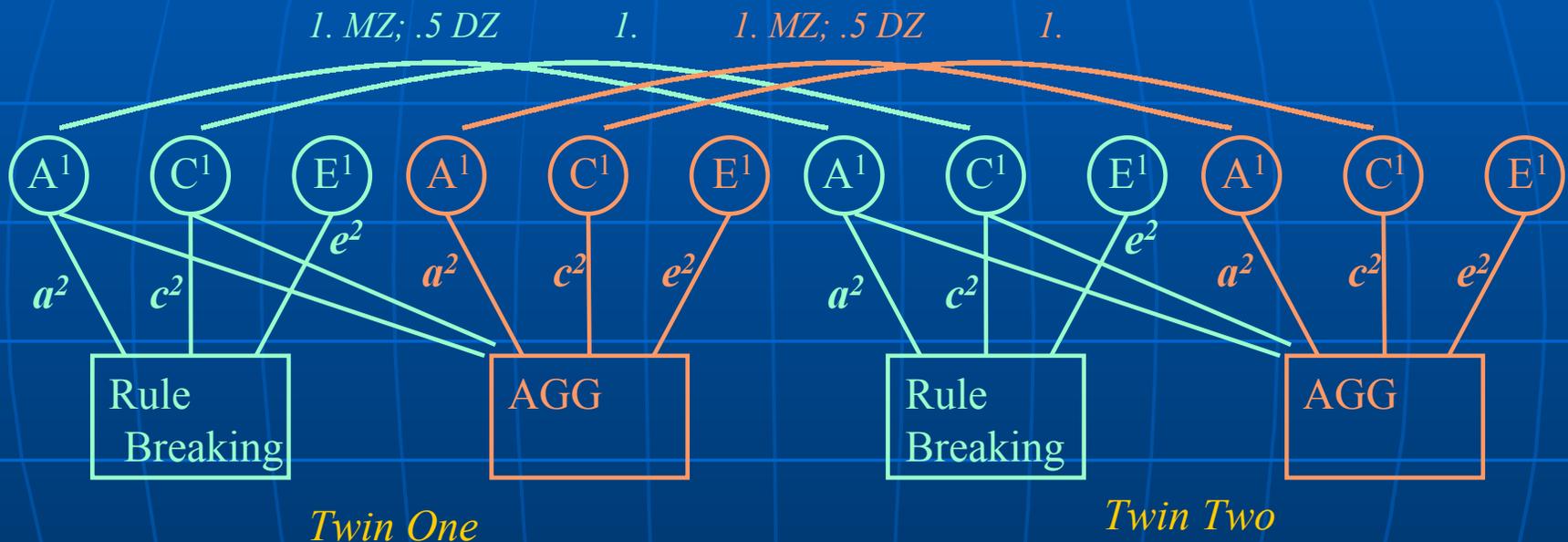
Co-occurrence of Aggressive Behavior and Rule-Breaking Behavior at Age 12: Multi-Rater Analyses

Bartels, M., Hudziak, J.J., Van den Oord, E.J.C.G.,
van Beijsterveldt, C.E.M., Rietveld, M.J.H., and
Boomsma, D.I.

Hudziak/Boomsma/Todd APA 2004 Rights
Reserved

- In press, Behavioral Genetics, 2003

Bivariate AGG, and RB



Data: CBCL, Bartels et al, In press, BG, 2003.

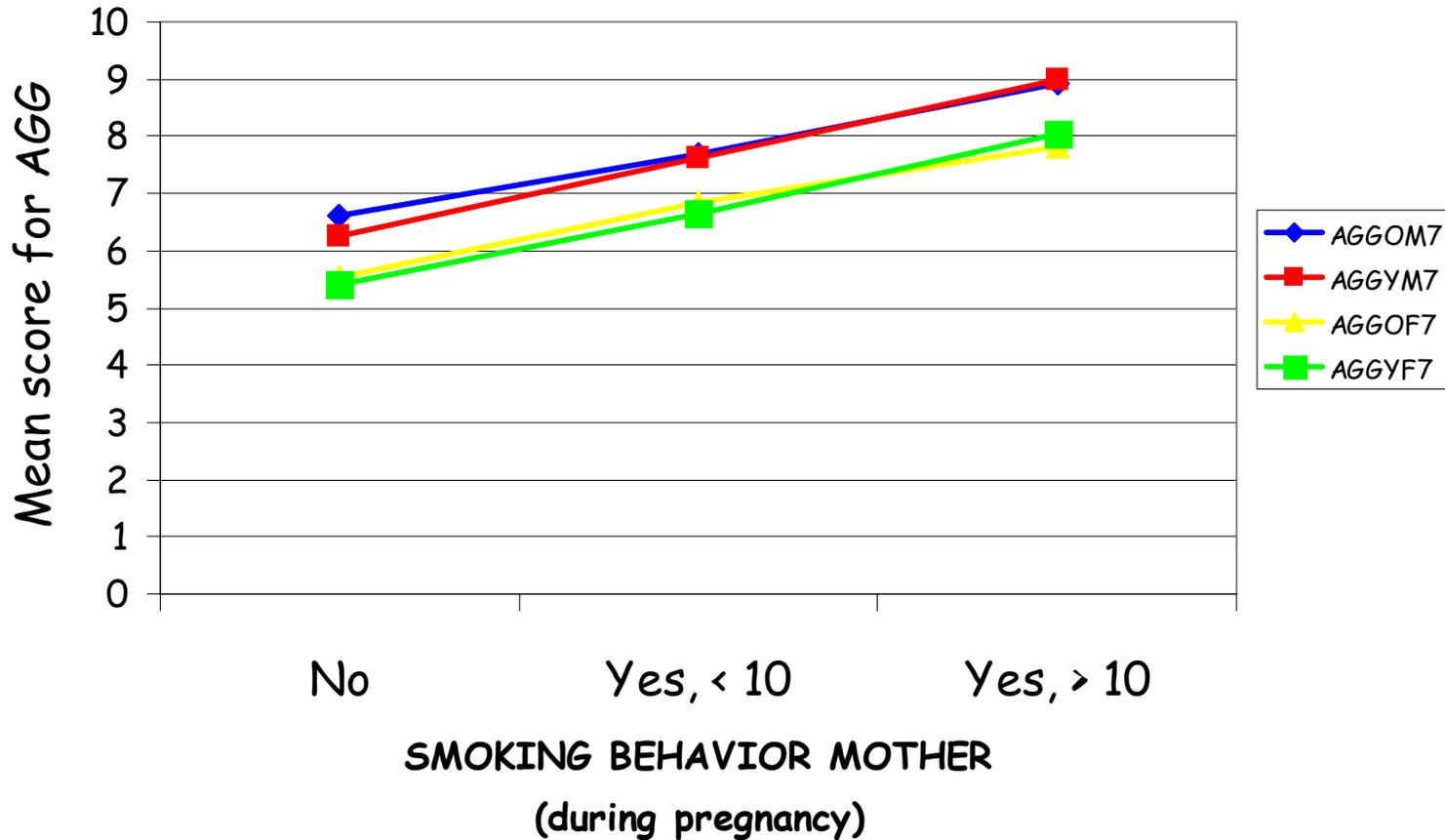
Genetics of Comorbidity between AGG and RB (ODD and CD for DSM Comparison).

- Genetic influences account for 79% and 69% of the individual differences in RB and AGG behavior (defined as AGG and RB on which both parents do agree) in boys. In girls 56% and 72% of the variance in RB and AGG are accounted for by genetic factors. **Shared environmental influences are significant for RB in girls only, explaining 23% of the total variance.**
- Eighty percent of the covariance between AGG and RB, similarly assessed by both parents, can be explained by genetic influences. So, co-occurrence in AGG and RB is mainly caused by a common set of genes.
- *Children who suffer AGG or RB in the clinical range are at equal risk to have the comorbid disorder as well. In our sample 50.0% to 63.9% of the children who are deviant on AGG are also deviant on RB and vice versa.*

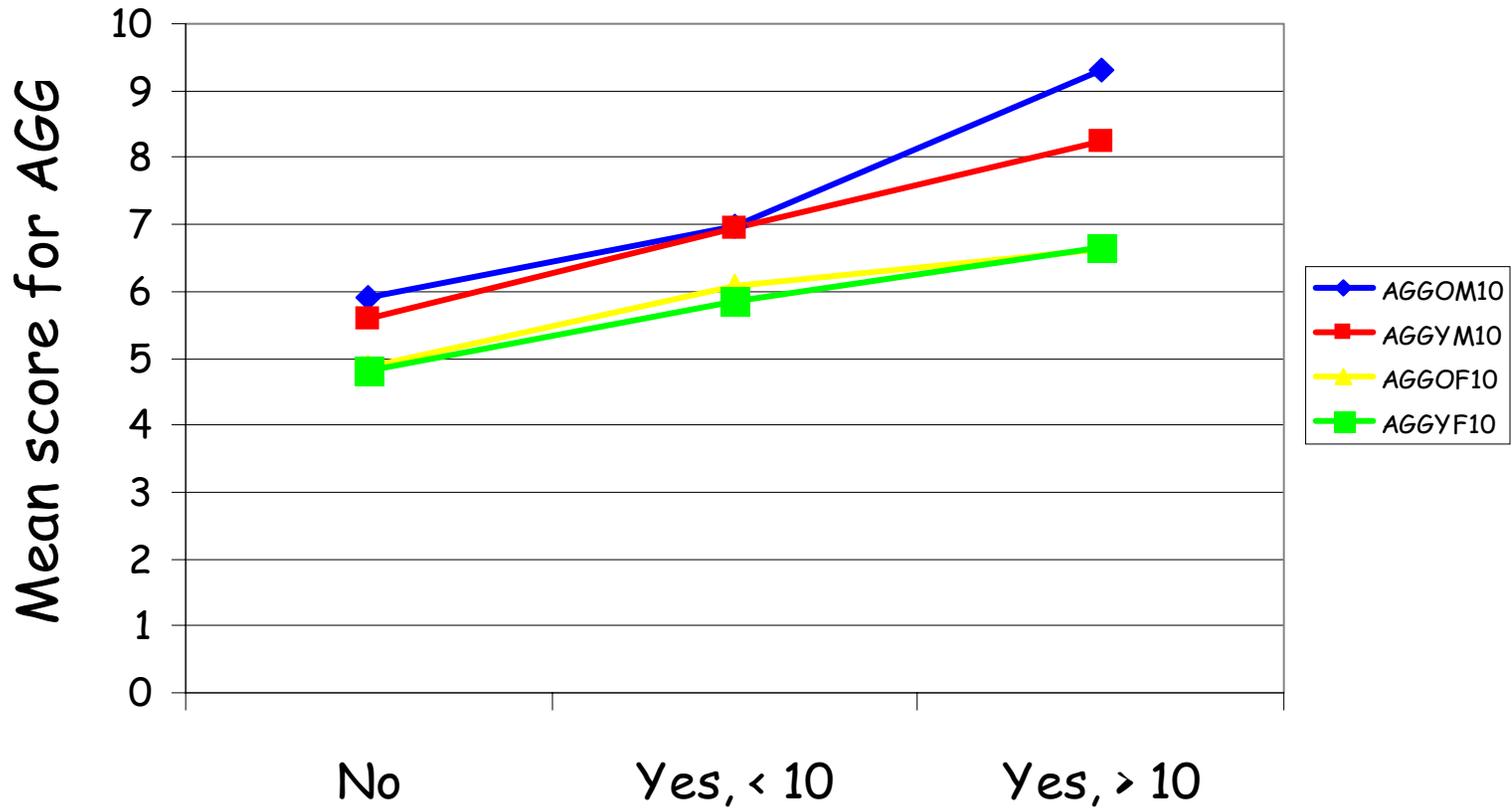
Maternal Risk Factors

- Again, for this meeting, our group ran analyses of maternal smoking behavior on measures of AP and AGG at each age.
- Smoking behavior for this work was obtained from parental interviews when the twins were born.
- Smoking data are:
 - Never smoked during pregnancy.
 - Did smoke
 - Less than 10 a day.
 - More than 10 a day.

Maternal smoking during pregnancy and Aggressive Behavior (CBCL) at age 7



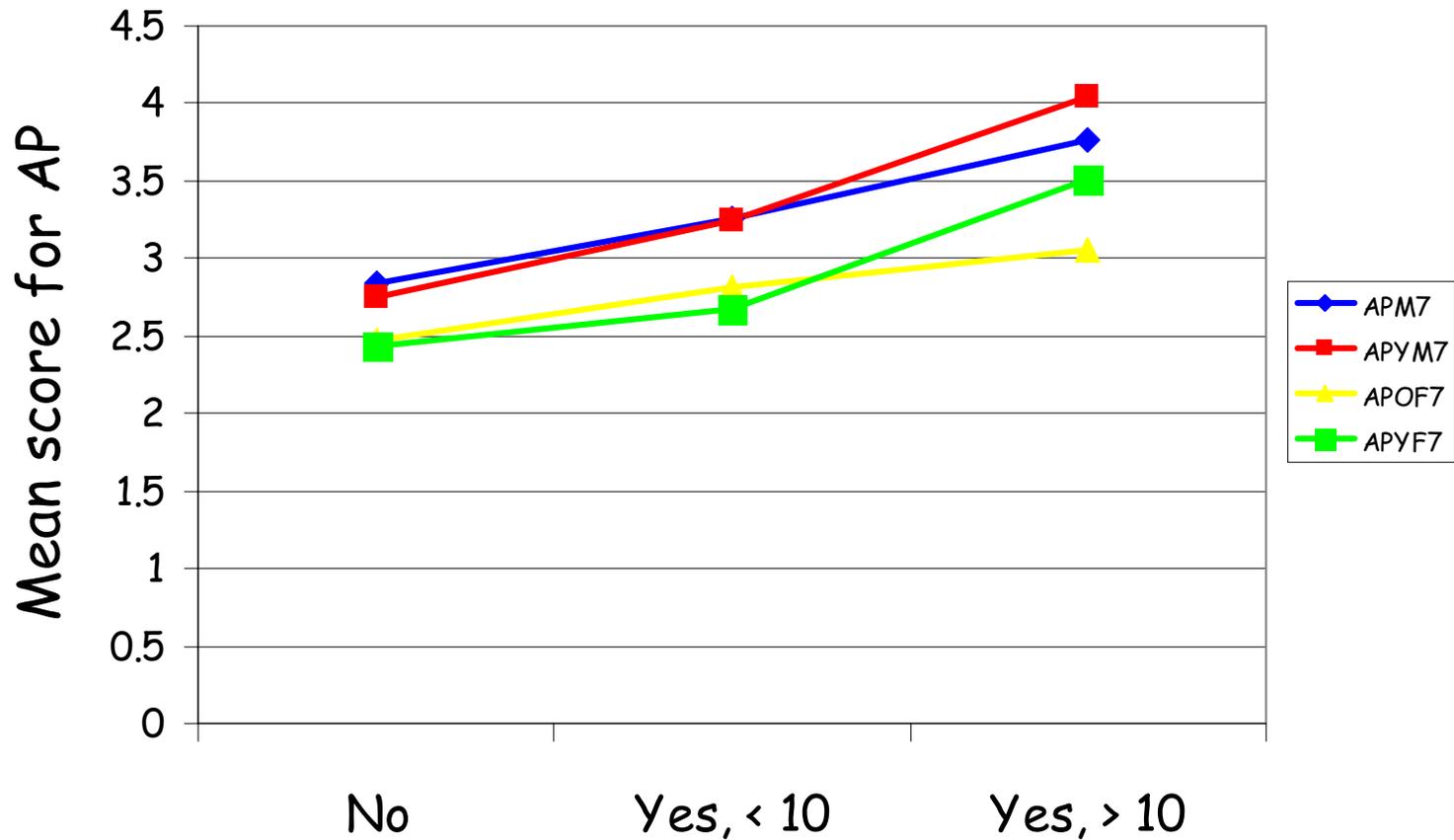
Maternal smoking during pregnancy and Aggressive Behavior (CBCL) at age 10



SMOKING BEHAVIOR MOTHER
(during pregnancy)

Hudziak/Boomsma/Todd APA
2004 Rights Reserved

Maternal smoking during pregnancy and Attention Problems (CBCL) at age 7



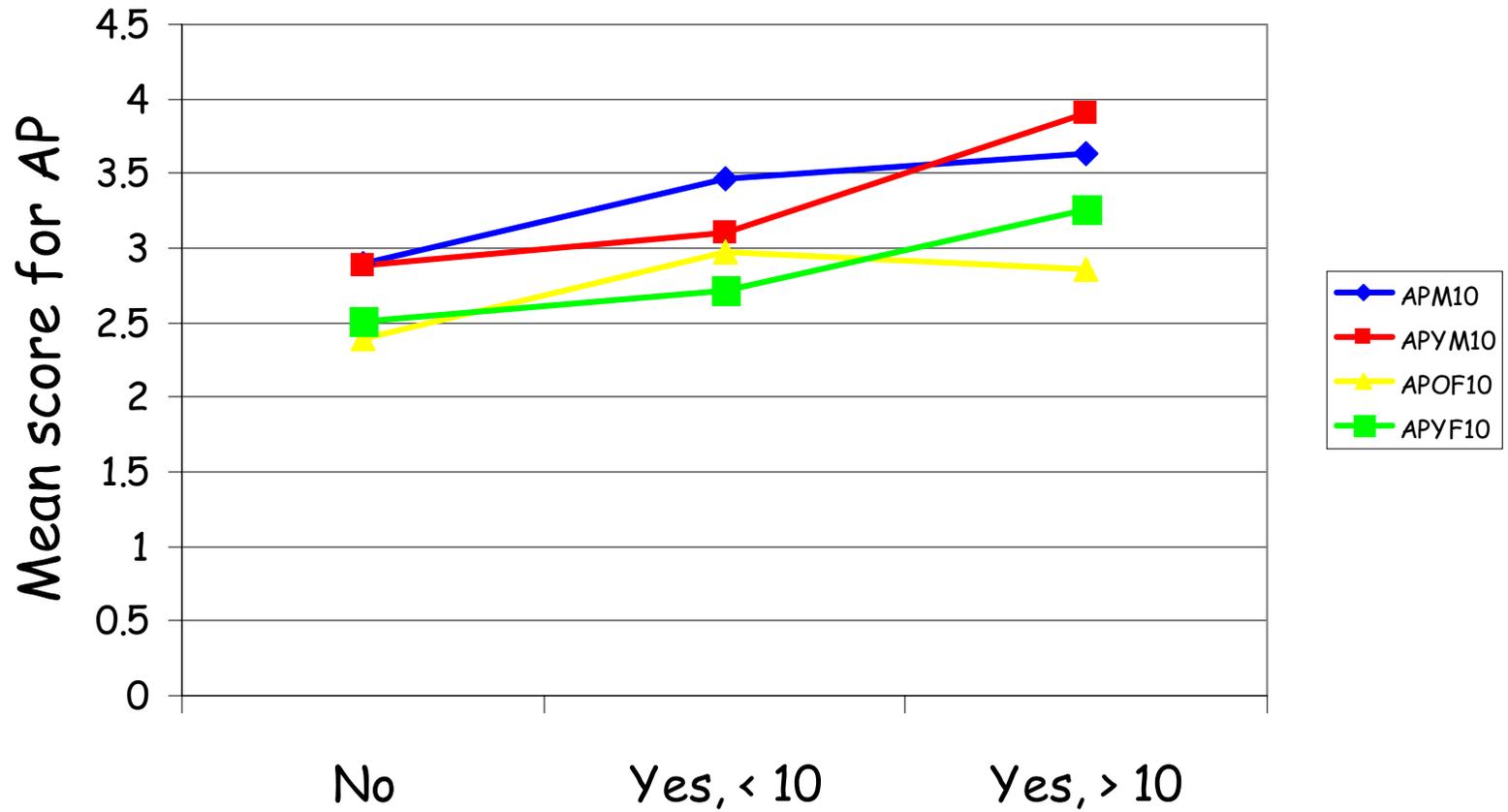
SMOKING BEHAVIOR MOTHER

(during pregnancy)

Hudziak/Boomsma/Todd APA

2004 Rights Reserved

Maternal smoking during pregnancy and Attention Problems (CBCL) at age 10



SMOKING BEHAVIOR MOTHER
(during pregnancy)

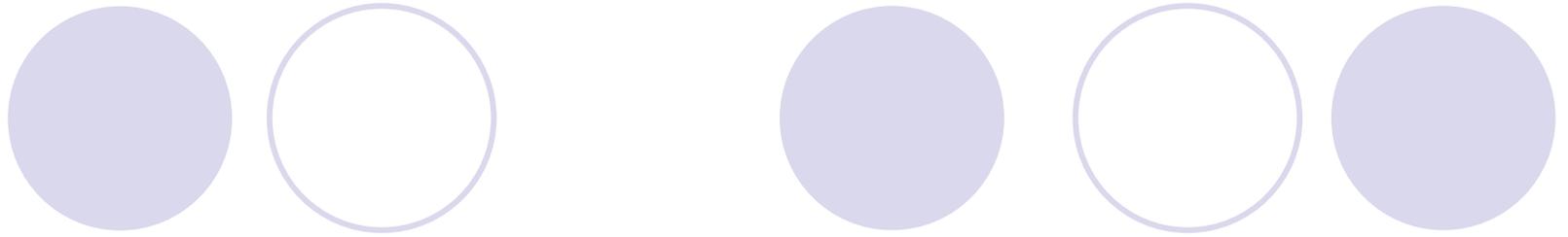
Hudziak/Boomsma/Todd APA
2004 Rights Reserved

Are longitudinal twin studies useful for the study of substance use?

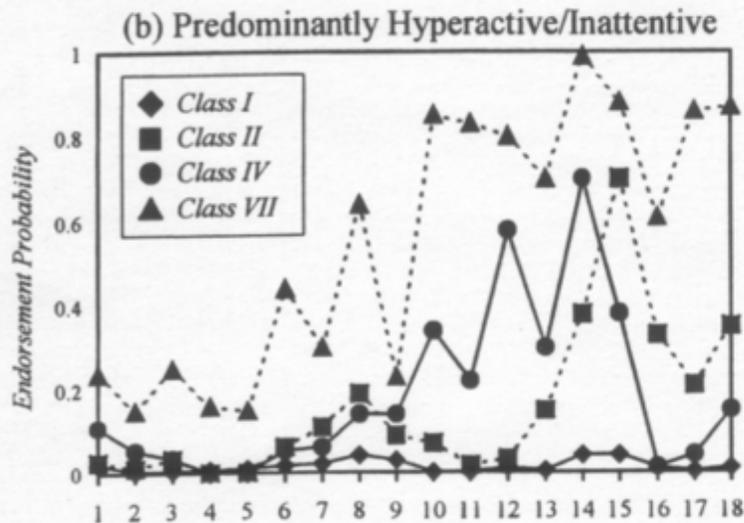
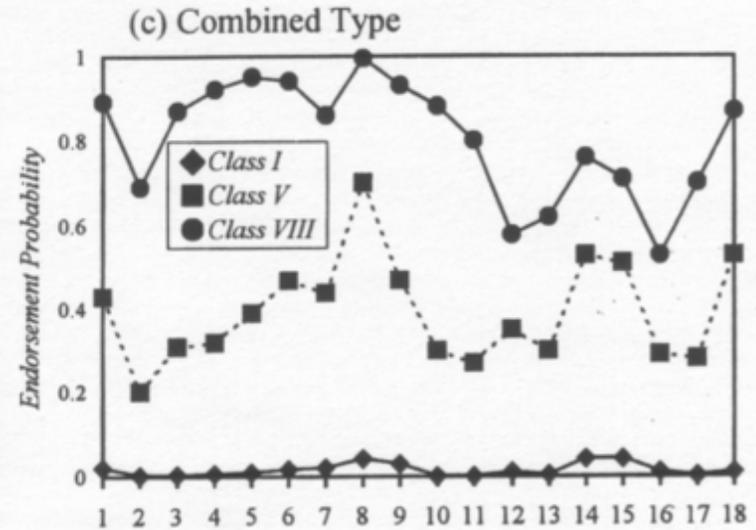
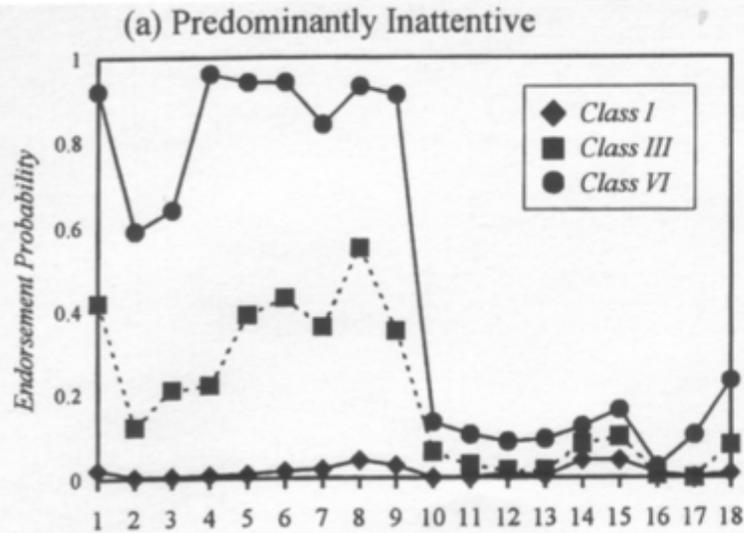
- We think so.
- Our twins are approaching peak age of initiation and regular use.
- Using persistent phenotypes may allow us to develop a strategy to identify not only those who are at greater risk to experiment, but also those who are at greater risk to abuse.

Discussion of DSM ADHD Studies

- These slides are provided by R. Todd et al.
- They focus on many analytic approaches we have used to test the relations between genetic and environmental factors on risk for ADHD and SUD.



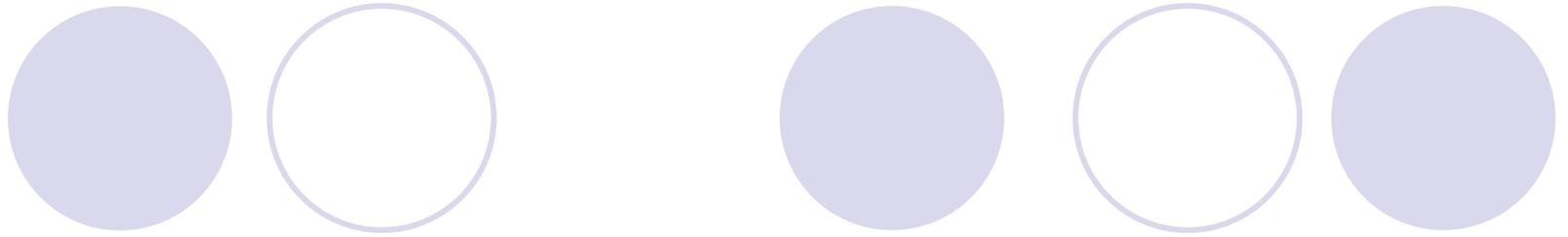
Latent Class Analysis And Heritability of ADHD



- | | |
|----------------------------|--------------------------------|
| 1. Inattention/careless | 10. Fidgets & squirms |
| 2. Sustaining attention | 11. Leaves seat |
| 3. Doesn't listen | 12. Runs or climbs |
| 4. Fails to finish | 13. Difficulty playing quietly |
| 5. Difficulty organizing | 14. Often on the go |
| 6. Sustained mental effort | 15. Talks excessively |
| 7. Loses things | 16. Blurts out |
| 8. Easily distracted | 17. Difficulty waiting |
| 9. Forgetful | 18. Interrupts |

Fig. 1 Latent class analysis of DSM-IV attention-deficit/hyperactivity disorder.

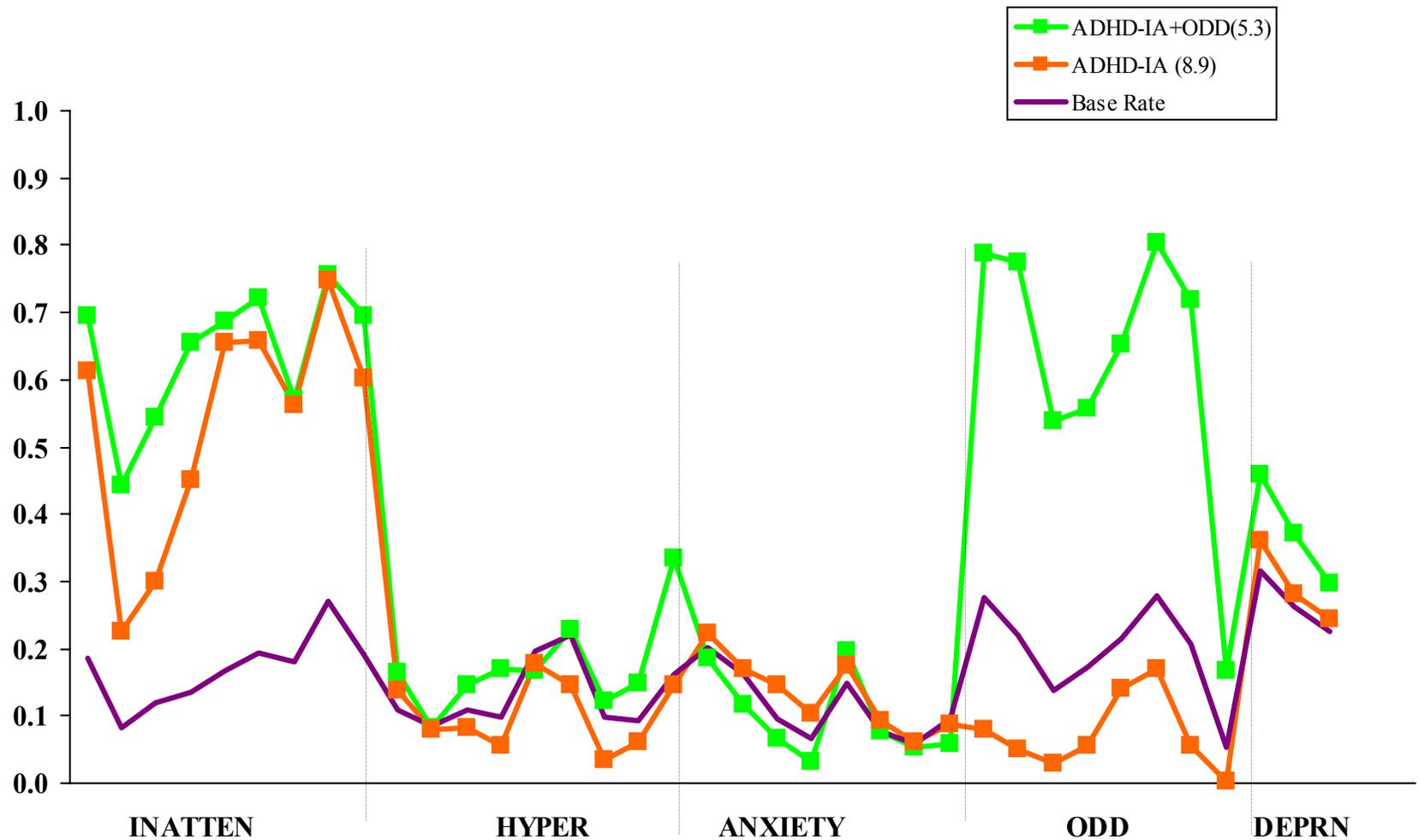
Hudziak et al., *J Am Acad Child Adolesc Psychiatry* 37:848-857, 1998.



Latent Class Analysis of Co-morbidity: ADHD, MDD, ODD and Anxiety

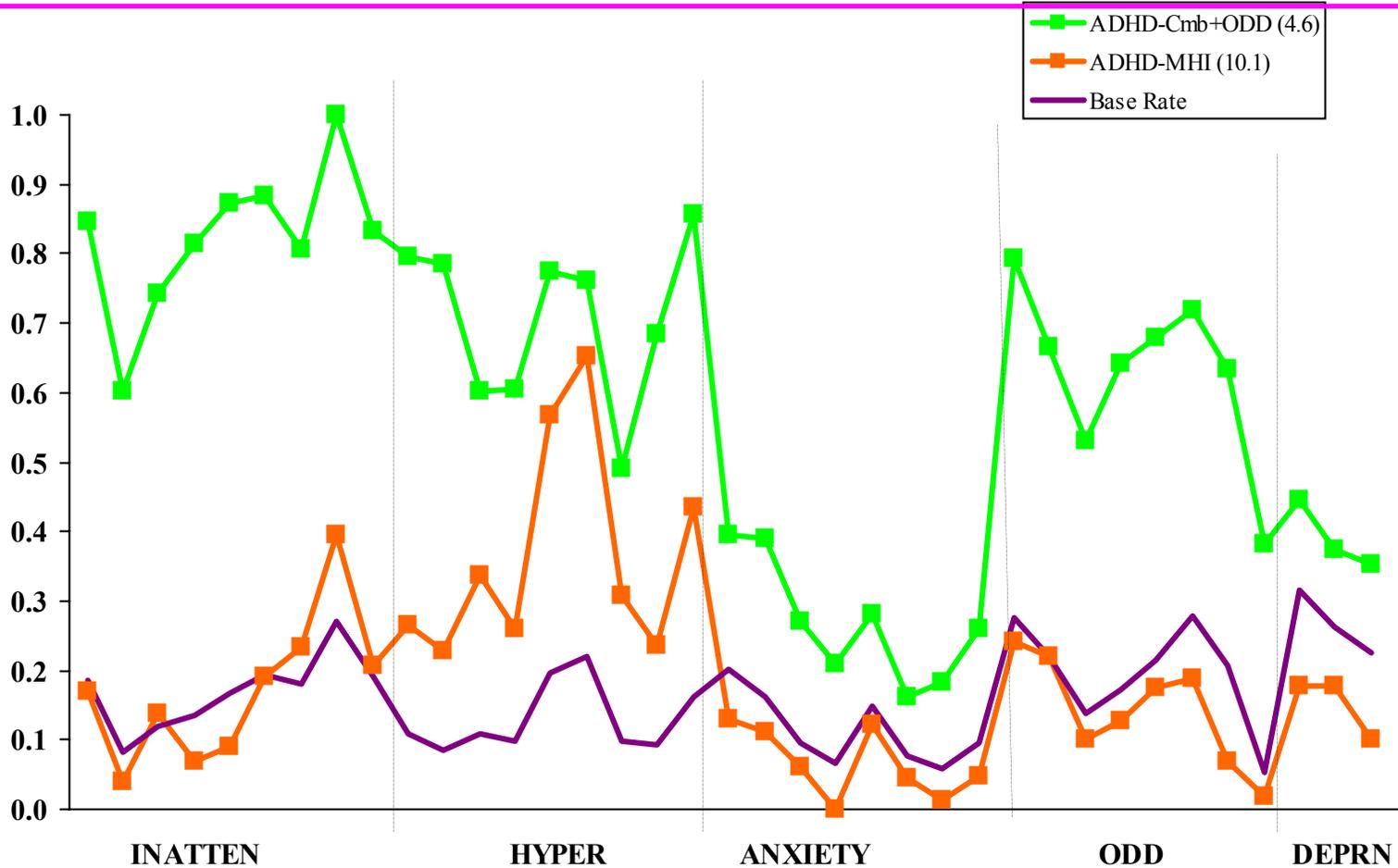
MOAFTS: N=2,904

Inattentive Classes

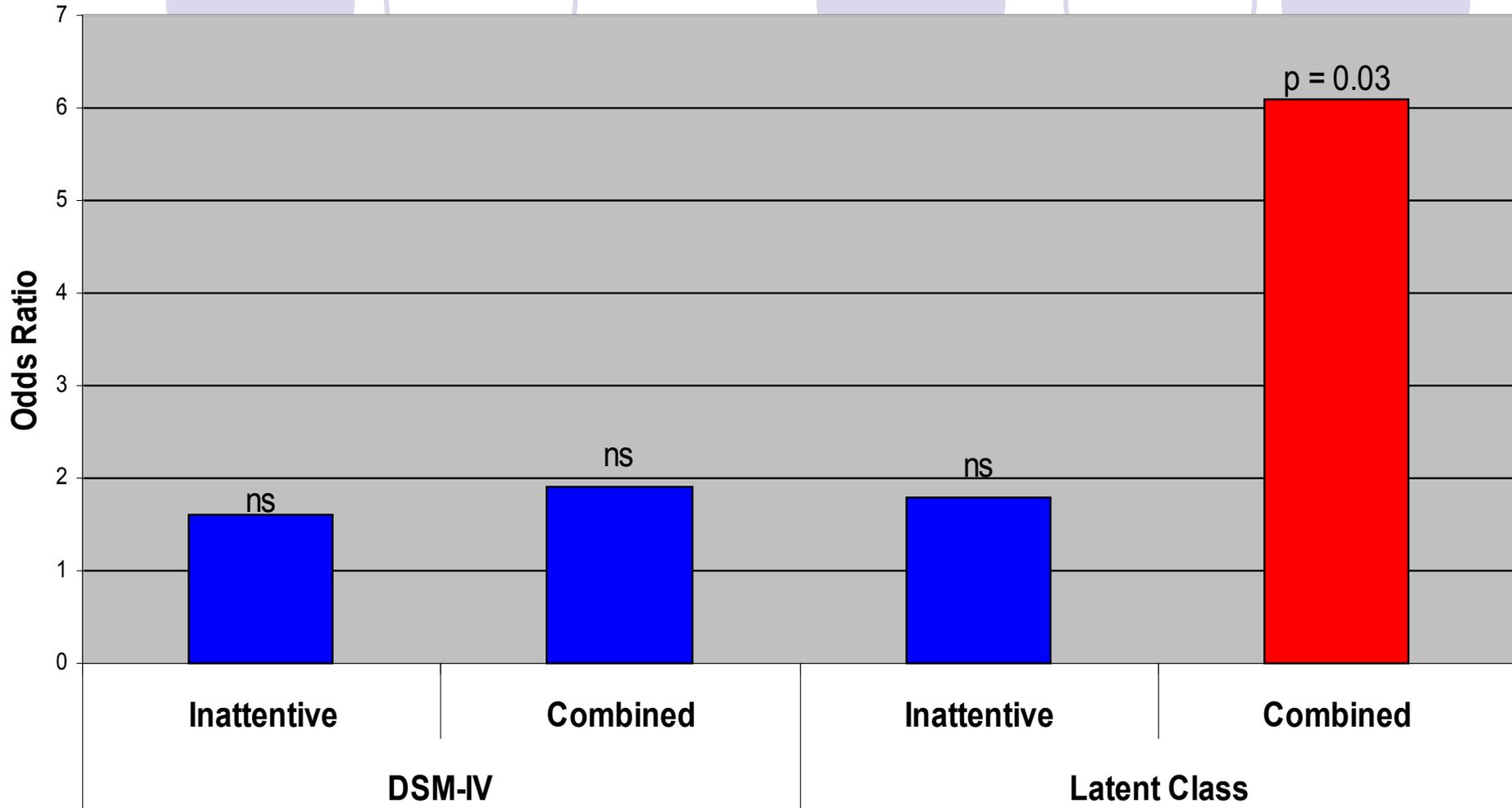


MOAFTS (N=2,904)

Combined, Mild Hyperactive-Impulsive Classes

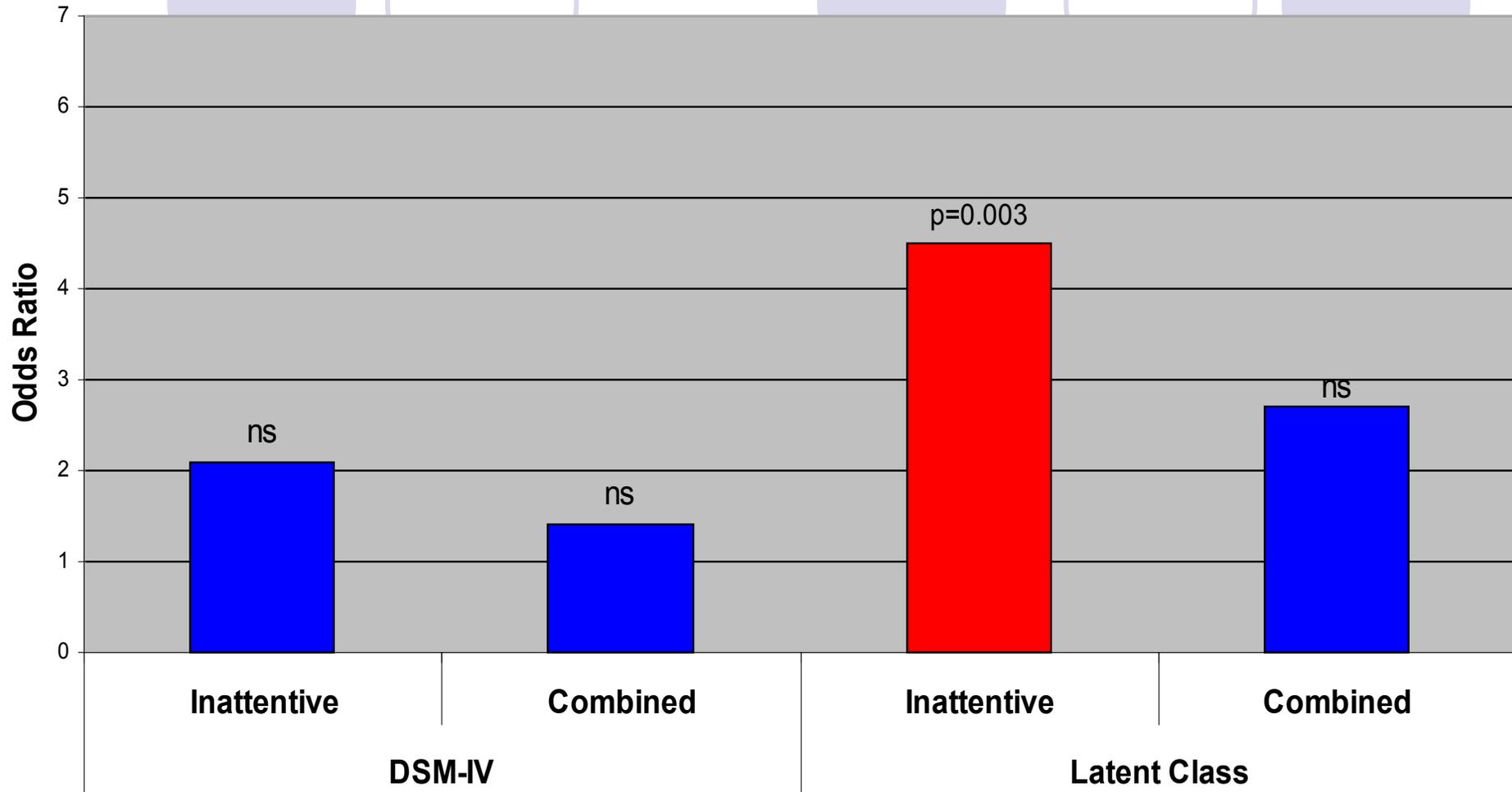


ADHD Predictors of Alcohol Abuse



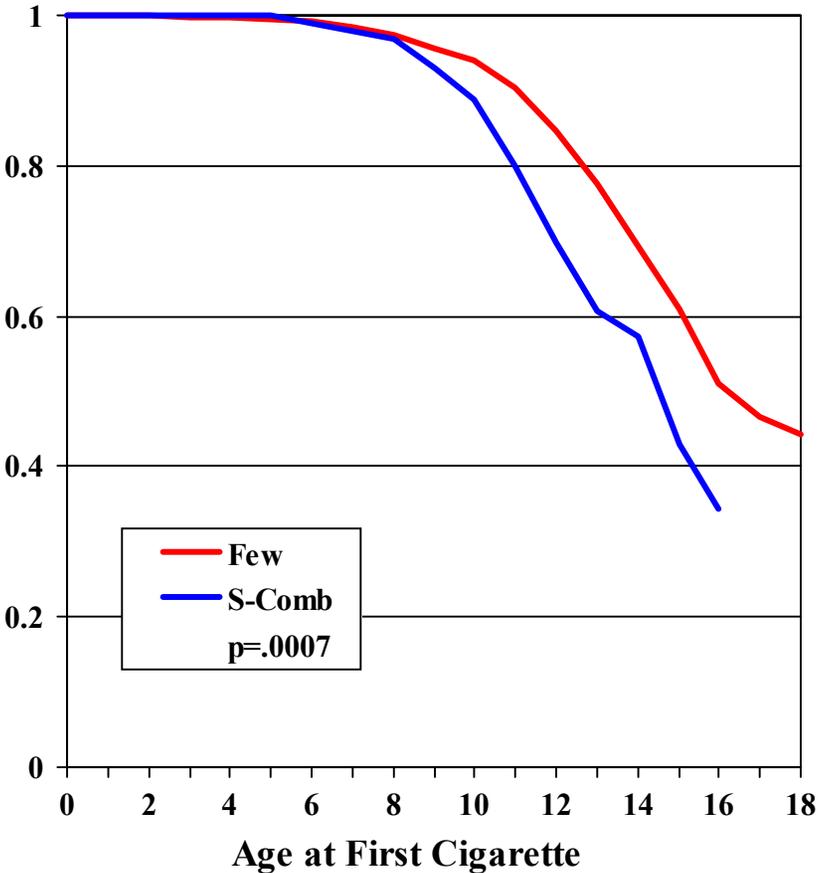
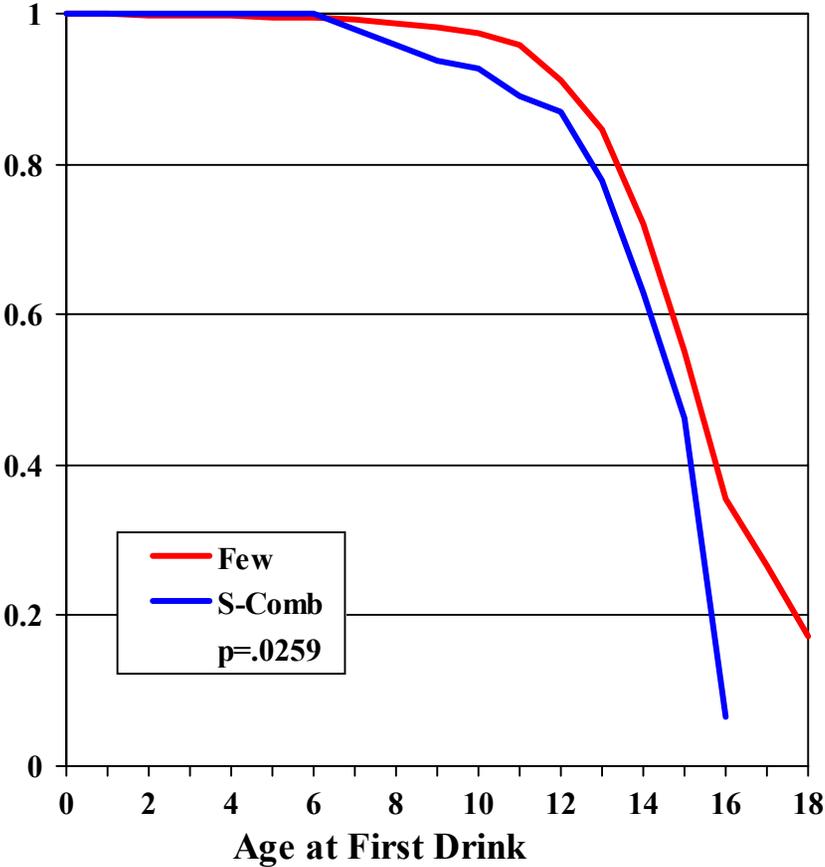
All values are adjusted odds ratios from multivariate logistic regression. Huber-White Robust estimators were used to correct for clustered data (i.e., twins). Covariates included sex, age, race, zygosity, smoking, marijuana usage, major depression, oppositional defiant disorder and conduct disorder. ns = not significant.

ADHD Predictors of Regular Smoking

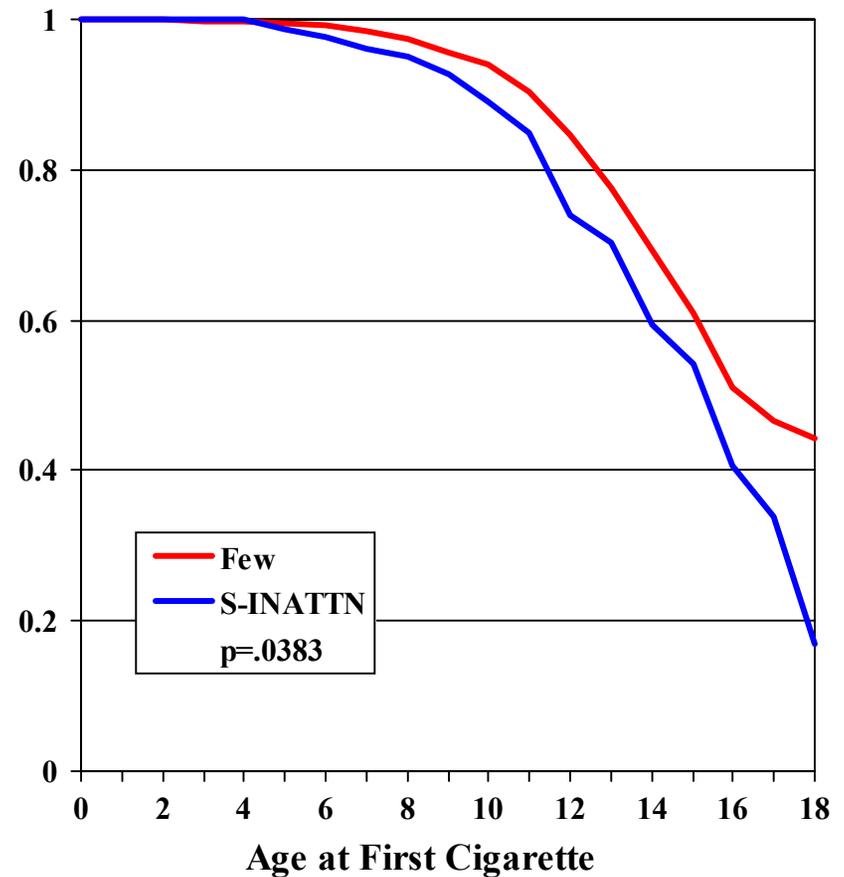
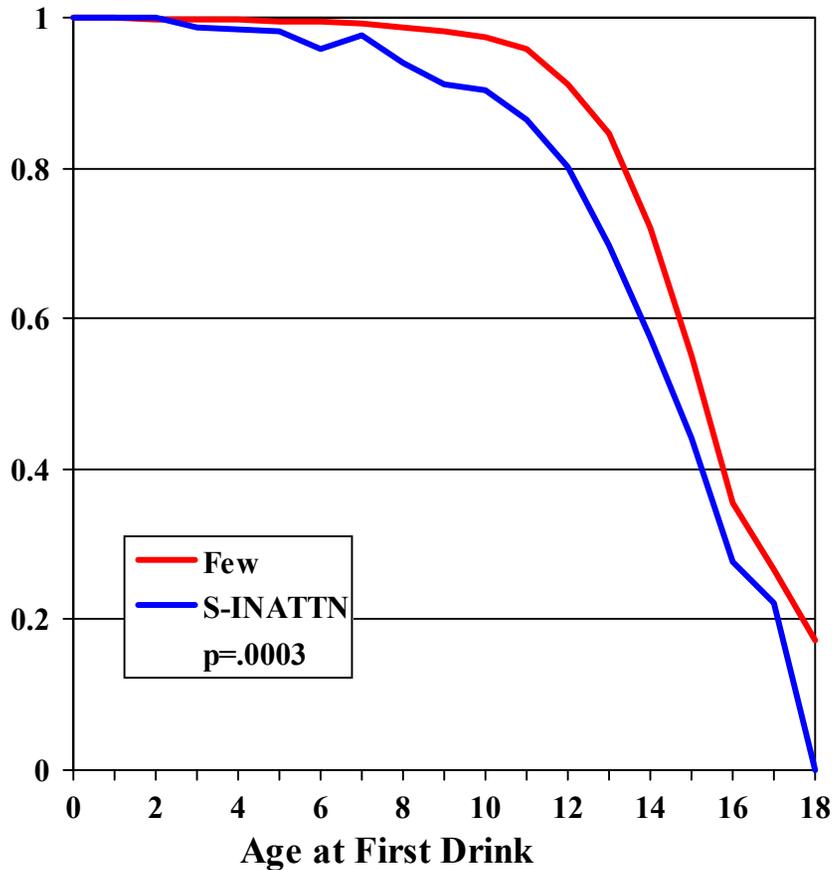


All values are adjusted odds ratios from multivariate logistic regression. Huber-White Robust estimators were used to correct for clustered data (i.e., twins). Covariates included sex, age, race, zygosity, alcohol abuse, marijuana usage, major depression, oppositional defiant disorder and conduct disorder. ns = not significant.

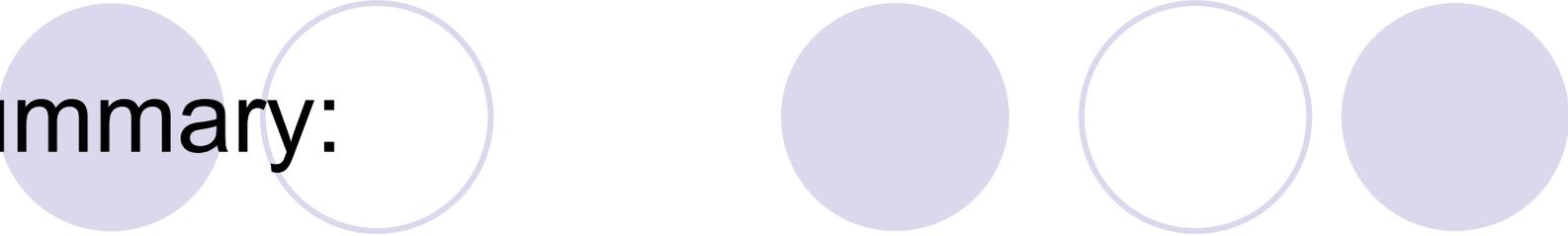
Kaplan-Meier Estimate of Survival Curves for Missouri Adolescents Aged 10-18 Years Stratified by Latent-Class Severe Combined Subtype



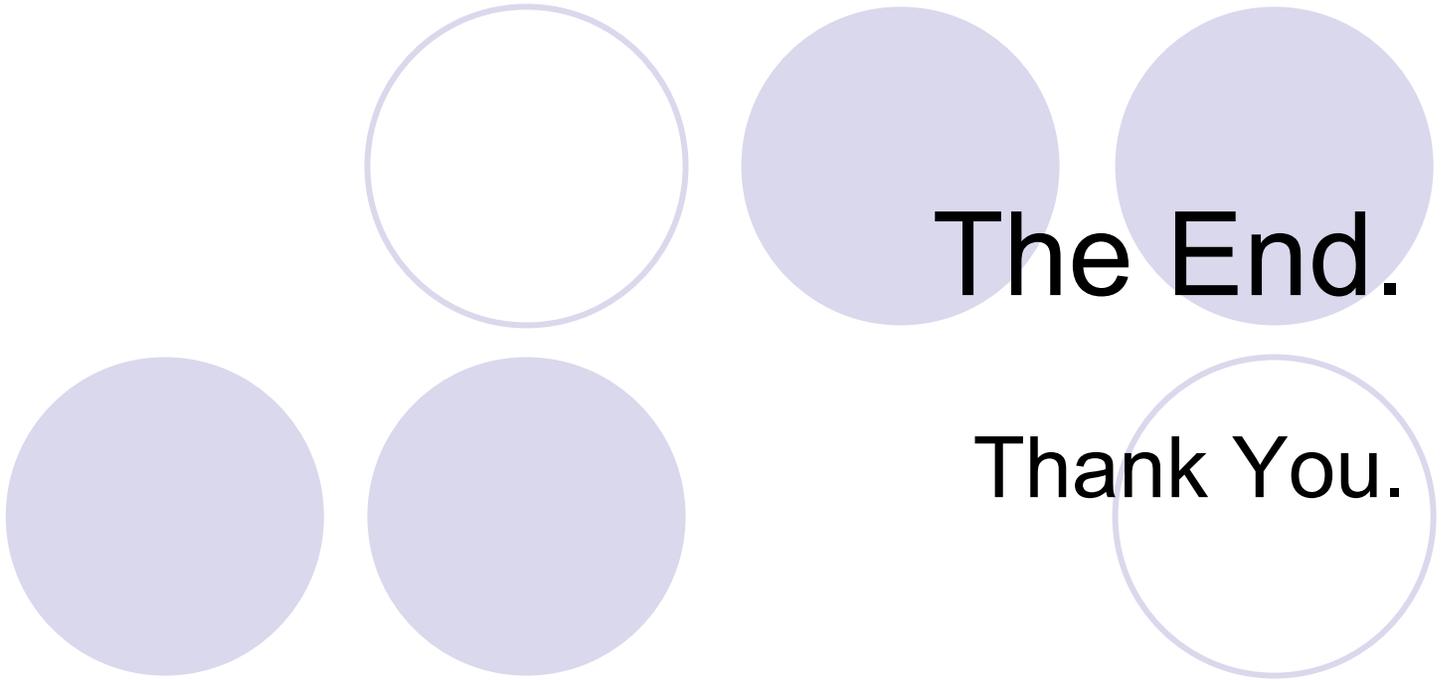
Kaplan-Meier Estimate of Survival Curves for Missouri Adolescents Aged 10-18 Years Stratified by Latent-Class Severe Inattention Subtype



Summary:



- We have identified children with highly deviant, persistent, and comorbid forms of AGG/RB and AP.
- We have used LCA and other novel approaches to the relations between DSM ADHD and SUD.
- A longitudinal twin approach may allow us to test these high risk, persistent phenotypes for initiation, abuse, and dependence studies.
- Use during pregnancy can be used as a covariate.
- Extended the twin model to a family design may then provide a model for considering both genetic and environmental contributions to initiation and persistence.



The End.

Thank You.